

INTRATHECAL NALBUPHINE IN DIFFERENT DOSES AS AN ADJUVANT TO SUBARACHNOID BLOCKAshoka Kumar Panigrahi¹, Bimal Krushna Panda², Alok Kumar Panigrahy³, Kulwant Lakra⁴, Sanjeeb Kumar Mishra⁵¹Associate Professor, Department of Pharmacology, VIMSAR, Burla, Odisha, India.²Associate Professor, Department of Anaesthesiology, VIMSAR, Burla, Odisha, India.³Trainee, Department of Critical Care and Medicine, AIIMS, New Delhi, India.⁴Assistant Professor, Department of Preventive and Social Medicine, VIMSAR, Burla, Odisha, India.⁵Junior Resident, Department of Preventive and Social Medicine, VIMSAR, Burla, Odisha, India.**ABSTRACT****BACKGROUND**

We searched for an ideal agent which can be universally used in all situations, easily available and cost effective with less side effects, so we studied the effect of nalbuphine a synthetic opioid analgesic that has both agonist and antagonist narcotic properties, added in different doses as an adjunct to bupivacaine and compared it with bupivacaine alone.

MATERIALS AND METHODS

Patients were randomly allocated into four groups. Each group consisted of 30 patients. They received either Bupivacaine 0.5% heavy (Group 1) or Groups (2, 3 and 4) received Bupivacaine 0.5% heavy with nalbuphine in dose range of .5 mg, .75 mg and 1 mg respectively. They were given the said drugs intrathecally in L3-L4 interspace with 25 G needle. Onset of motor and sensory loss was noted before positioning the patient. Intraoperative monitoring of fluid management was done depending on the blood loss and haemodynamic parameters. Two segment regression time of sensory blockade was assessed, and pain was assessed by VAS at the time of 1st pain medication.

RESULTS

The mean onset time of sensory block of Group 3 and 4 was significantly early as compared to the onset of sensory block as compared to Group 1 and 2. The quality of analgesia provided with addition of nalbuphine in Group 2, 3 and 4 is significantly good as compared to bupivacaine group alone. Two segment regression of sensory blockade, duration and the quality of analgesia was significantly prolonged by addition of intrathecal nalbuphine and was significantly more in Group 4 as compared to other groups.

CONCLUSION

From our study, we conclude that for spinal anaesthesia 1 mg of nalbuphine when added to 0.5% hyperbaric bupivacaine provides excellent analgesia with longer duration of action and minimal side effects.

KEY WORDS

Bupivacaine, Nalbuphine, Intrathecal.

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BACKGROUND

The surgical stress response peaks during the post-operative period and has major effects on almost all body systems. A pain-free and stress-free post-operative period definitely helps in early mobilisation and recovery, thereby reducing morbidity and mortality. Different adjuncts such as opioids, alpha-2 agonists, neostigmine, midazolam, adenosine, ketamine, epinephrine and magnesium sulphate have been used with local anaesthesia. Out of which intrathecal opioid like morphine, fentanyl, sufentanil and alfentanil are widely used.^(1,2,3,4) We searched for an ideal agent which can be universally used in all situations, easily available and cost effective with less side effects. We studied the effect of nalbuphine, a synthetic opioid analgesic that has both agonist and antagonist narcotic properties, added in different doses as an adjunct to bupivacaine and compared it with bupivacaine alone.

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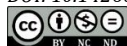
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**MATERIALS AND METHODS**

After obtaining approval from ethical committee, a double-blind randomised controlled clinical study was conducted on 120 adult patients admitted to VSS Medical College, Burla during a period of Oct 2012 – Sep 14 for lower abdominal and orthopaedic procedures under subarachnoid block. Patients were randomly allocated into four groups. Each group consists of 30 patients. They received either of drug solution as 3 mL.

Group-I: Bupivacaine 0.5% heavy, 2.5 mL plus NS 0.5 mL (3 mL).

Group-II: Bupivacaine (0.5%) heavy, 2.5 mL plus nalbuphine 0.5 mg and NS (3 mL).

Group-III: Bupivacaine (0.5%) heavy, 2.5 mL plus nalbuphine 0.75 mg and NS (3 mL).

Group IV: Bupivacaine 0.5% heavy, 2.5 mL plus nalbuphine 1 mg and NS (3 mL).

Preparation of Drug

Nalbuphine ampoules (1 mL) contains nalbuphine HCL 10 mg/mL and Bupivacaine 0.5% heavy ampoules containing bupivacaine HCL 5 mg/mL were used for the study. Ten units of nalbuphine taken in an insulin syringe and diluted to 40 units, so in 40 units contains 2.5 mg of nalbuphine. Eight units contain 0.5 mg, 12 units contain 0.75 mg and 16 units contain 1 mg.

Inclusion Criteria

1. American Society of Anesthesiologists (ASA) I and II patients.
2. Age group of 17 - 45 years.
3. Patient with written valid consent.
4. Patient undergoing elective lower abdominal and orthopaedic surgery.

Exclusion Criteria

1. Infection at the site.
2. Bleeding disorder.
3. Allergic reaction to any anaesthetic drug.
4. ASA III and IV grade.
5. Patients on tranquilisers, hypnotics, sedatives and other psychotropic drugs.

Preparation of Patient

The patients were explained about the procedure in layman’s terms and an informed consent was obtained. The patients were kept nil per oral after midnight and on the day of operation. All patients were given tab. Diazepam 5 mg orally on the previous night and also in the morning, about an hour before surgery with a sip of water. Under all possible aseptic measures, lumbar puncture was done in L3-L4 interspace with 25-G needle. After obtaining a free flow of CSF, the drug was injected at a rate of 0.2 mL/sec. After injecting the drug, needle was withdrawn, and puncture site was sealed with sterile dressing. The patient was turned supine, onset of motor and sensory loss was noted before positioning the patient. The surgeons were allowed to start the operation. Intraoperative fluid requirements given as necessary depending on the blood loss and haemodynamic parameters. Intraoperative hypotension and bradycardia was managed with IV Ephedrine, Phenylephrine and Atropine respectively. In case of any respiratory depression, oxygen is administered through face mask at a rate of 3 L/min. Advanced equipment and drugs for resuscitation, airway management and ventilation were kept ready.

The following Parameters were noted and used for Comparison between the Groups

- a. Time of onset of sensory block (i.e. time taken from intrathecal injection of drug to time to complete loss of sensation to pin pricks).
- b. Hypotension, bradycardia and respiratory depression.
- c. Duration of effective analgesia [i.e. time of onset of sensory block to the first request of analgesia (VAS > 3)].
- d. Quality of analgesia.
- e. Incidence of side effects like nausea, vomiting, urinary retention and itching.
- f. Sedation was monitored for 24 h by Campbell scoring 1- Wide awake; 2- Sedated, but easily arousable; 3- Drowsy, difficult to arouse; 4-Unarousable.

Pain was assessed by VAS at the time of 1st pain medication. Patient was given a scale marked from 0 to 10 and were asked to mark on a scale the degree of pain he or she experienced ranging from no pain at 0 to maximum pain at 10 point. At the time of rescue analgesia, quality of analgesia was assessed by asking the patient to give a global assessment of overall effectiveness of the analgesic treatment. When VAS > 3, rescue analgesia with Inj. diclofenac sodium was given and study ended.

Statistical Analysis

Statistical analyses were done using Kruskal-Wallis test, Chi-square test, One-Way ANOVA and Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA; version 16 for Windows). P-value of 0.05 or less was considered as significant.

RESULTS

Groups	Sex		Weight (kg)	Height (cm)	Age (Yrs.)		
	Male	Female			15-25	26-35	36-45
1	15	15	59.3	162.46	11	9	10
2	16	14	59.53	161.96	9	14	7
3	14	16	59.13	161.73	13	12	5
4	16	14	58.76	162.00	13	11	6

Table 1. Distribution of Patients according to Age, Sex, Weight and Height

All the four groups were comparable according to Age, Sex, Weight and Height.

Group	Onset of Sensory Block	SD	Two Segment Regression Time of Sensory Blockade (Minutes)	SD	Duration of Analgesia (Minutes)	SD
1	74 sec	0.07	119.20	4.20	169.10	4.6
2	67 sec*	0.063	133.26*	4.14	214.80*	4.37
3	58 sec*	0.14	140.79*	4.24	236.96*	3.93
4	55 sec*	0.18	153.73*	4.20	277.56*	3.94

Table 2. Onset of Sensory Block, Two Segment Regression Time of Sensory Blockade and Duration of Analgesia

*The mean difference is significant at the 0.05 level.

The mean onset time, two segment regression of sensory blockade and duration of analgesia in nalbuphine groups were statistically significant in comparison to bupivacaine alone group. Amongst the nalbuphine groups, intergroup parameters when compared were statistically significant in all the groups and maximum adjudged was group 4.

Group	Onset of Motor Blockade (Minutes)	SD	Duration of Motor Block	SD
1	5.72	0.167	138.40	4.6
2	5.68	0.197	139.46	4.37
3	5.67	0.200	140.76	3.93
4	5.61	0.204	143.26	3.94

Table 3. Onset of Motor Blockade and Duration of Motor Block

Onset of motor blockade and the duration of motor block was comparable in all four groups.

Score	Pain Relief	Group 1	Group 2	Group 3	Group 4
0	No	0	0	0	0
1	Poor	5	1	0	0
2	Fair	15	20	15	12
3	Good	10	9	15*	18*

Table 4. Quality of Analgesia

*The mean difference is significant at the 0.05 level.

The quality of analgesia provided with addition of nalbuphine in Group 3 and 4 is significant.

Groups	Nausea and Vomiting	Urinary Retention	Pruritus	Resp. Depression
1	2	2	0	0
2	3	2	2	0
3	4	3	3	0
4	4	3	3	0

Table 5. Side Effects

Adverse effects like nausea, vomiting, urinary retention, pruritus and respiratory depression were statistically insignificant.

Sedation Score	Group 1	Group 2	Group 3	Group 4
1	28 (93.33%)	7 (23.33%)	5 (16.66%)	4 (13.33%)
2	2 (6.67%)	23 (76.66%)	25 (83.33%)	24 (80%)
3	Nil	Nil	Nil	2 (6.67%)
4	Nil	Nil	Nil	Nil

Table 6. Sedation Score

Most of the patients had sedation score 1 in Group I, while most of the patients had sedation score 2 where nalbuphine was used as an adjunct.

DISCUSSION

Nalbuphine, a mixed agonist-antagonist drug, binds both to mu and kappa receptors, but its action on these receptors is divergent. When nalbuphine binds to μ receptor, it serves only to competitively displace other μ agonists from the receptor without itself displaying any agonist activity similar to those of naloxone. However, when it binds to kappa receptor, it has agonist activating effect. This pattern of binding and effects defines nalbuphine as a mixed agonist-antagonist. The rationale for the combination of opioids and local anaesthetics is that these two types of drugs eliminate pain by acting at two different sites. Local anaesthetics act at the nerve axon and the opioid at the receptor site in the spinal cord.^[4,5] The major site of action of opioid is within the second and third laminae of substantia gelatinosa in the dorsal horn of the spinal cord.

Nalbuphine, administered intrathecally, binds to kappa receptors in the brain and spinal cord areas which are involved in nociception, producing analgesia and sedation without μ side effects. Intrathecal opioids used as adjuncts are capable of producing analgesia of prolonged duration, but allow early ambulation of patients because of their sympathetic and motor nerve-sparing activities. The popularity of intrathecal opioids was undermined by reports of side-effects such as respiratory depression, pruritus and postoperative nausea and vomiting. Nalbuphine given systemically has a reduced incidence of respiratory depression and has been used to antagonise the side-effects of spinal opiates. Intrathecal nalbuphine causes significant analgesia accompanied by minimal pruritus and respiratory depression.^[6,7,8,9,10]

In our study, all the four groups were comparable in distribution of patients according to age, sex, weight, height and duration of surgery. The mean onset time of sensory block of Group 3 and 4 was significantly early onset of sensory block as compared to Group 1 and 2. Two segment regression of sensory blockade was significantly prolonged by addition of intrathecal nalbuphine as seen in Group 2, 3

and 4 when compared with Group 1 bupivacaine alone. Also, the mean two segment regression time was significantly more in Group 4 as compared to Group 3 and 2. The duration of analgesia was significantly prolonged with addition of nalbuphine as compared with bupivacaine alone. Duration of analgesia was maximum in Group 4 and was significant to Group 2 and 3 and also the duration of analgesia in Group 3 was significantly more as compared to Group 2 and Group 1. The quality of analgesia provided with addition of nalbuphine in Group 2, 3 and 4 is significantly good as compared to bupivacaine group alone. The quality of analgesia provided by Group 4 is statistically significant as compared to other groups. Adverse effects like nausea, vomiting, urinary retention, pruritus and respiratory depression were statistically insignificant. Most of the patients had sedation score 1 in bupivacaine alone group, while most of the patients had sedation score 2 where nalbuphine was used as an adjunct. The incidence of bradycardia is more in Group 2 and 3 as compared to Group 1 and Group 4, but it is non-significant. Similarly, the incidence of hypotension is slightly more in nalbuphine group, but it is statistically insignificant.

CONCLUSION

From our study, we found that nalbuphine hydrochloride when added to 0.5% hyperbaric bupivacaine for intrathecal administration, prolongs the duration of sensory blockade, provides excellent quality of analgesia and longer duration of post-operative analgesia with minimal side effects. From our study, we conclude that for spinal anaesthesia 1 mg of nalbuphine when added to 0.5% hyperbaric bupivacaine provides excellent analgesia with longer duration of action and minimal side effects.

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